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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,529	11/26/2001	Jeffry D. Watkins	P-IX 4976	2007

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,529	WATKINS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 42-63* is/are pending in the application.

4a) Of the above claim(s) *4-16,18-20 and 44-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17,21,22,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041115*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 12, 2004, is acknowledged and has been entered. Claims 1, 3, 17, 21, 22, 42, and 43 have been amended.

2. Claims 1-22 and 42-63 are pending in the application. Claims 4-16, 18-20, and 44-63 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention or species of invention, there being no allowable generic or linking claim.

3. Claims 1, 2, 17, 21, 22, 42, and 43, insofar as the claims are drawn to the elected species of invention, are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

5. At pages 16 and 17 of the amendment filed November 12, 2004, Applicant has affirmed the election with traverse to prosecute the invention of claims 1-22 and 42, insofar as the claims are drawn to the species of antibody comprising SEQ ID NOs: 45, 155, 63, 157, 22, and 77.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The Examiner thanks Applicant for correctly noting that claim 20 was inadvertently omitted from the listing of claims withdrawn from further consideration set forth in the previous Office action.

Applicant has requested that withdrawn process claims be rejoined in accordance with the provisions of MPEP § 821.04. The examiner has required restriction between product and process claims and Applicant has elected claims

directed to the product. Where Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Information Disclosure Statement

6. The information disclosure filed November 12, 2004 has been considered. An initialed copy is attached hereto.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, the amendment filed November 12, 2004 has obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed May 11, 2004.

For clarity of record, although Applicant's arguments traversing the provisional obviousness-type double patenting rejection set forth in section 23 of the previous Office action are noted and considered, the rejection has been withdrawn for the following reason:

Copending Application No. 09/478,977 discloses and claims humanized (grafted) antibodies that bind to a cryptic collagen epitope and inhibit angiogenesis, including the disclosed monoclonal antibodies HUI77 and HUIV26 (see the specification of the copending application at, e.g., page 23, lines 9 and 10; and page 38, line 1, through page 39, line 10). Although the instant application discloses the same monoclonal antibodies (see the instant specification at, e.g., page 19, line 9, through page 20, line 9), the instant claims are drawn to a grafted antibody or functional fragment thereof that binds a cryptic collagen epitope and comprises a variant of a CDR of either the light or the heavy chain variable domain of monoclonal antibody HUIV26. The monoclonal antibodies described in the copending application comprise SEQ ID NOs: 26, 28, 30, 20, 22, and 24 without variation or SEQ ID NOs: 38, 40, 42, 32, 34, or 36 without variation. In contrast, the antibodies claimed in this application do not comprise each of these CDRs, since at least one of the CDRs must differ from that of the parent antibody by at least one amino acid. Accordingly, the subject matter of claims of the copending application does not anticipate the subject matter of the instant claims.

Grounds of Rejection Maintained

Claim Rejections – 35 USC § 112

8. The rejection of claims 1, 2, 17, 21, and 22, and claims 42 and 43, insofar as the claims are drawn to the antibody of any of claims 1, 2, 17, 21, and 22, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This ground of rejection is set forth in section 17 of the previous Office action mailed May 11, 2004.

At pages 20-23 of the amendment filed November 12, 2004, Applicant has traversed this ground of rejection, arguing that the specification teaches numerous antibodies having the required specificity. Furthermore, citing *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004), Applicant has asserted that the written description requirement is met by the description "a fully characterized antigen", either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository. Therefore, because the specification describes the claimed antibodies as binding specifically to denatured collagen, Applicant has asserted the written description requirement is thus met. Moreover, Applicant has cited additional case law to support the assertion that because the claimed antibodies can be distinguished from others by mere routine experimentation, the written description requirement is met.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As noted in the previous Office action, WO 00/40597 A1, Xu et al. (*Hybridoma* **19**: 375-385, 2000), Wheatcroft et al. (*Matrix Biol.* **18**: 361-372, 1999), Kalluri et al. (*Proc. Assoc. Am. Physicians* **108**: 134-139, 1996), Borza et al. (*J. Biol. Chem.* **275**: 6030-6037, 2000), Nakanishi et al. (*Kidney Int.* **46**: 1413-1421, 1994), Yoshioka et al. (*Am. J. Pathol.* **144**: 986-996, 1994), and David et al. (*J. Biol. Chem.* **276**: 6370-6377, 2001) each teach an antibody, which binds a cryptic collagen epitope. Although each binds a cryptic collagen epitope, the Examiner has no factual evidence that any of the antibodies disclosed by the prior art comprises a light chain variable domain comprising a light chain CDR selected from the group consisting of SEQ ID NOs: 157, 22, and 77, or a heavy chain variable domain comprising a heavy chain CDR selected from the

group consisting of SEQ ID NOs: 45, 155, and 63, as does the elected species of invention (i.e., an antibody that comprises SEQ ID NOs: 45, 155, 63, 157, 22, and 77).

Notably, since the instant specification does not describe the antibodies that are disclosed by the prior art as binding specifically to a cryptic collagen epitope, the question arises, how can the claimed antibodies be distinguished from the antibodies disclosed by the prior art?

Applicant has asserted that the description of a fully characterized antigen to which the claimed antibodies bind would reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed; however, the claims are drawn to a genus of antibodies that bind to "a cryptic collagen epitope", not to a well characterized antigen. The epitope, Greenspan (of record) teaches is a three-dimensional structure characteristic of an antigen to which an antibody binds, including amino acid residues within the structure that are contacted by amino acid residues of the antibody, even if those contacts be energetically neutral or destabilizing to binding. The "cryptic collagen epitope" to which the claimed antibodies bind has not been described.

Moreover, native collagen is well characterized, but the claims are drawn to a genus of antibodies that bind to an epitope of a denatured collagen molecule that is evidently a structural feature lacking or less exposed in native collagen, since the antibodies bind specifically to the denatured molecule without binding the native molecule. Denaturation, usually caused by heat, acids, bases, detergents, or certain chemicals such as urea, is a gross structural change in a protein; although still composed of the same polymer of amino acids, denatured proteins lose their three-dimensional structure and thus their characteristic folded structure. The damage caused by denaturation is often irreversible; and denatured proteins can be rendered insoluble as a result of the loss of higher order secondary, tertiary, and quaternary structures. As a result of its denaturation, collagen looses its native conformation and adopts a different, uncharacterized structure that displays antigenic determinants or epitopes that were not present in the structure of the native molecule. Because of these gross structural changes in the molecule caused by its denaturation, some antibodies

that bind the native molecule do not bind the denatured molecule, and some antibodies that bind denatured collagen do not bind native collagen. There is evidence in the art that denatured proteins are heterogeneous in structure, as might be expected. For example, autoantibodies to produced in patients with certain autoimmune syndromes are heterogeneous in their epitope specificities, recognizing both conformational and linear determinants. Accordingly, although Applicant has asserted that the antigen to which the claimed antibodies bind is well characterized, to the contrary, it is expected that denatured collagen is actually structurally heterogeneous, such that not every molecule of any given preparation of denatured collagen is expected to display the epitope to which the claimed antibodies bind.

Therefore, it is submitted that denatured collagen cannot be fully characterized by its structure or its functional properties. Furthermore, because the denatured collagen molecule to which the claimed antibodies cannot be meaningfully described, *or distinguished* by formula or chemical name, and Applicant has not deposited a sample of the denatured protein to which the claimed antibodies bind in a public depository, it does not appear that denatured collagen can be adequately described, so as to provide an adequate description of the claimed antibodies.

Applicant has argued that the claimed antibodies can be readily distinguished from other antibodies because of their ability to bind a cryptic epitope displayed by denatured collagen; however, as mentioned above, the prior art teaches other antibodies that also bind to a cryptic collagen epitope. These antibodies cannot be readily distinguished from the claimed antibodies by simply comparing their ability to bind denatured collagen, because each of the antibodies binds specifically to a cryptic collagen epitope. Furthermore, as noted in the previous Office action, even using a competition assay, the skilled artisan cannot immediately distinguish the claimed antibodies from others because, although other antibodies may not bind the same epitope, they may bind a spatially overlapping epitope and are therefore capable of sterically hinder binding of the claimed antibody.

Also noted in the previous Office action, although claim 17 is drawn to a genus of antibodies or functional fragments thereof comprising six complementarity determining

regions (CDRs) of an antibody known to bind collagen, even relatively small changes in the structure of the antibody can change the way in which an antibody binds an antigen; such small changes thus alter the "epitope" to which an antibody binds.

Contrary to Applicant's assertion that the claimed antibodies can be distinguished from others by mere routine experimentation, absent a detailed description of the epitopes or epitopes to which the claimed antibodies bind, the skilled artisan could immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus of antibodies that bind a cryptic collagen epitope. As evidenced by Greenspan, the structure of an epitope cannot be predicted; it must be determined empirically. The empirical determination of an epitope does not constitute merely routine experimentation.

In conclusion, the written description requirement set forth under 35 U.S.C. § 112, first paragraph, has not been met, since the supporting disclosure would not reasonably convey that Applicant had possession of the claimed invention at the time the application was filed.

9. The rejection of claims 1, 2, 21, and 22, and claims 42 and 43, insofar as the claims are drawn to the antibody of any of claims 1, 2, 21, and 22, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a grafted antibody, or a functional fragment thereof, antibody or functional fragment binds specifically to collagen, wherein said antibody or functional fragment comprises the three heavy chain CDRs of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77, does not reasonably provide enablement for making a grafted antibody, or a functional fragment thereof, which antibody or functional fragment binds specifically to a cryptic collagen epitope, wherein said antibody or functional fragment comprises only one or two heavy chain CDRs or wherein said antibody or functional fragment comprises only one or two light chain CDRs is maintained. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This ground of rejection is set forth in section 18 of the previous Office action mailed May 11, 2004.

At pages 24 and 25 of the amendment filed November 12, 2004, Applicant has traversed this ground of rejection, arguing that "the claims specify only the number of recited CDRs present in the antibody and that the total number of CDRs present is specified by that which is known to those of skill in the art" (page 24, paragraph 3). Applicant has stated that the specification need not describe, and best omits, that which is well known in the art. That the claimed antibodies would contain at least 6 CDRs is made evident by the teachings in the specification, since the specification teaches how to make a grafted antibody comprising three of the disclosed light chain CDRs and three of the disclosed heavy chain CDRs, which has the ability to bind specifically to cryptic collagen epitope.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims have been given the broadest reasonable interpretation that is both consistent with the supporting disclosure and consistent with the interpretation that the skilled artisan would reach.

Applicant has argued that the skilled artisan would understand that an antibody necessarily comprises at least six CDRs. Even though the claims are so limited, the previous Office action states that the skilled artisan would not reasonably expect an antibody comprising fewer than three light chain CDRs or fewer than three heavy chain CDRs to bind to an antigen, since Mariuzza et al. teaches that each of the six CDRs contribute to the "antigen-binding site" of the antibody; but the issue that is raised in the rejection is somewhat different: The specification does not provide sufficient guidance and direction to enable the skilled artisan to make an antibody that binds to a cryptic collagen epitope, which comprises a light chain variable domain comprising fewer than three of the disclosed light chain CDRs or a heavy chain variable domain comprising fewer than three of the disclosed heavy chain CDRs, which Applicant has shown can be

used to make an antibody that binds to the epitope. As Applicant has remarked, the specification teaches a plurality of antibodies that bind specifically to a cryptic collagen epitope; however, each of these antibodies comprises a light chain variable domain comprising three of the disclosed light chain CDRs and a heavy chain variable domain comprising three of the disclosed heavy chain CDRs. It would not be expected, for example, that combining any of the variants of CDR1 of monoclonal antibody HUIV26 and any of the variants of CDR2 or CDR3 will always produce an antibody that binds the denatured collagen. While not every combination of the disclosed light chain CDRs or heavy chain CDRs is expected to produce a functional antibody that binds a cryptic collagen epitope, the claims can embrace some non-working embodiments. However, the claims also encompass antibodies that bind a cryptic collagen epitope comprising only one or two of the disclosed CDRs. It is these antibodies that cannot be made by the skilled artisan without undue experimentation, since amount of guidance and direction disclosed in the supporting specification would not be sufficient to enable the artisan to readily make these antibodies by mere routine experimentation, because one cannot predict which other CDRs can be used instead of the disclosed CDRs to produce a functional antibody that binds a cryptic collagen epitope.

Since it appears that Applicant did not intend to claim an antibody comprising a light chain variable domain comprising fewer than three of the disclosed light chain CDRs or comprising a heavy chain variable domain comprising fewer than three of the disclosed heavy chain CDRs, it is submitted that the claims be rewritten to more particularly claim the subject matter that Applicant actually regards as the invention. For example, claim 1 could perhaps be rewritten to read: A grafted antibody or functional fragment thereof that binds to a cryptic collagen epitope comprising a variant of a CDR selected from the group consisting of SEQ ID NOS: 26, 28, 30, 20, 22, and 24, wherein said variant of a CDR differs from the CDR by at least one amino acid.

10. The rejection of claims 1, 42, and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

This ground of rejection is set forth in section 20 of the previous Office action.

At pages 25 and 26 of the amendment filed November 12, 2004, Applicant has remarked that it is believed that the amendment to claim 1 has resolved this issue; however, claim 1 presently recites, "comprising one or more complementarity determining regions (CDRs) having at least one amino acid substitution in a CDR". A CDR does not "have" a CDR; rather, a CDR is a CDR.

This issue may be remedied by amending claim 1 to recite, for example, "comprising one or more complementarity determining regions (CDRs) selected from the group consisting of SEQ ID NOS: 26, 28, 30, 20, 22, and 24, wherein said one or more CDRs has at least one amino acid substitution and said grafted antibody or functional fragment thereof [...]".

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 11, 2005

LARRY R. HELMS, PH.D
PRIMARY EXAMINER